Lung Cancer 136 (2019) 52–56

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

A phase II study of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab in the first-line treatment of patients with stage IV squamous non-small cell lung cancer

Liza C. Villaruz[a,*], Manuel Cobo[b], Konstantinos Syrigos[c], Dimitrios Mavroudis[d], Wei Zhang[e], Jong Seok Kim[e], Mark A. Socinski[a]

[a] UPMC Hillman Cancer Center, Pittsburgh, PA, USA
[b] Hospital Regional Universitario de Malaga, Malaga, Spain
[c] National & Kapodistrian University of Athens, Athens, Greece
[d] University General Hospital of Heraklion, Heraklion, Greece
[e] Eli Lilly and Company, Indianapolis, IN, USA

ARTICLE INFO

Keywords:
Squamous non-small cell lung cancer (NSCLC)
Necitumumab
Epidermal growth factor receptor (EGFR)
nab-paclitaxel
Carboplatin
NCT00981058

ABSTRACT

Objectives: Necitumumab is a second-generation, recombinant, human IgG1-type monoclonal antibody directed against EGFR approved for adult patients with metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine and cisplatin. This study assessed the efficacy and safety of albumin-bound paclitaxel (*nab*-paclitaxel) and carboplatin in combination with necitumumab as first-line therapy in patients with stage IV squamous NSCLC.

Materials and methods: The treatment regimen comprised triplet induction with necitumumab (800 mg) with *nab*-paclitaxel (100 mg/m^2) and carboplatin (AUC 6 mg*min/mL) for 4 cycles, followed by doublet maintenance with necitumumab and nab-paclitaxel with a 3-weekly schedule until progressive disease or unacceptable toxicity. The primary endpoint of the study was objective response rate (ORR).

Results: Fifty-four patients were enrolled. Median age was 65 years (range, 47–80 years). The majority of the patients were male (n = 42 [77.8%]) with an ECOG PS of 1 (n = 42 [77.8%]). The ORR was 51% (n = 26/54), and the disease control rate was 78.4% (n = 40/54). Median overall survival (OS) was 15.5 months (95% confidence interval [CI]: 10.18–not calculable), and the OS rate at 12 months was 50.4% (95% CI: 29.0–68.4). Median progression-free survival was 5.6 months (95% CI: 4.24–7.69)]. The most frequently reported treatment-emergent adverse events were anemia (57.4%), fatigue (55.6%), neutrophil count decreased (55.6%), hypomagnesemia (44.4%), and rash (38.9%).

Conclusion: Necitumumab/*nab*-paclitaxel/carboplatin first-line therapy produced favorable efficacy outcomes with manageable toxicity in patients with stage IV squamous NSCLC. The safety profile was fairly comparable with previous necitumumab combination studies in lung cancer.

1. Introduction

Squamous cell carcinoma, characterized by large keratinizing and atypical polygonal cells in the respiratory bronchial epithelium [1], affects 30% of patients with lung cancer [2]. Historically, patients with squamous NSCLC were treated with first-line platinum-based chemotherapy [3]. Unlike non-squamous NSCLC, there have been no validated, targetable oncogenic drivers to date. The development and recent approval of targeted immunotherapies, either alone or in combination with platinum-doublet chemotherapy based on improved overall survival, offer a new treatment approach for patients with advanced squamous NSCLC [4,5]. However, platinum-based chemotherapy is the preferred treatment option for patients with squamous NSCLC tumors with high tumor proportion scores after disease progression on first-line pembrolizumab monotherapy [3]. In addition, there remains an unmet need for patients with squamous NSCLC who are ineligible for immunotherapy due to pre-existing autoimmunity, solid organ transplant, or prior immune-related toxicity.

Activated epidermal growth factor receptor (EGFR) induces downstream signalling through signal transduction pathways that mediate

* Corresponding author at: UPMC Hillman Cancer Center, 5150 Centre Avenue, Pittsburgh, PA, 15232, USA.
E-mail address: villaruzl@upmc.edu (L.C. Villaruz).

https://doi.org/10.1016/j.lungcan.2019.08.009
Received 15 March 2019; Received in revised form 28 June 2019; Accepted 13 August 2019

cell proliferation, cell survival, and cell migration, thereby contributing to neoplastic transformation and tumor growth [6,7]. Targeted monoclonal antibodies binds to EGFR and block ligand-induced phosphorylation of EGFR, thus inhibiting its activation and downstream signaling [4].

Necitumumab, a second-generation, recombinant, fully human IgG1-type monoclonal antibody directed against EGFR, was recently approved in the US and EU for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin [8–10]. In the phase III SQUIRE study (NCT00981058), the combination of necitumumab plus gemcitabine and cisplatin as first-line therapy showed a statistically significant advantage over the same chemotherapy alone in overall survival (OS), progression-free survival (PFS), and disease control rate (DCR) in patients with stage IV squamous NSCLC [11].

Paclitaxel protein-bound particles for injectable suspension (albumin-bound), *nab*-paclitaxel, demonstrated statistically significant advantages over solvent-based paclitaxel when combined with carboplatin in terms of objective overall response rate (ORR), PFS, and OS [12]. Because *nab*-paclitaxel was significantly advantageous for patients with squamous NSCLC in terms of best ORR and improved PFS and OS, it was approved as first-line therapy for locally advanced or metastatic NSCLC [12].

Taken together, results from the SQUIRE and *nab*-paclitaxel studies were the impetus for this phase II study assessing the efficacy and safety of *nab*-paclitaxel and carboplatin in combination with necitumumab as first-line therapy in patients with stage IV squamous NSCLC.

2. Methods

2.1. Study design and patients

In this single-arm, phase II study (NCT02392507), necitumumab (800 mg) plus *nab*-paclitaxel (100 mg/m^2) [13] and carboplatin (AUC 6 mg*min/mL) [14] chemotherapy (triplet regimen) was administered via intravenous infusion for a maximum of four 3-week cycles, or until there was radiographic documentation of progressive disease (PD), toxicity requiring cessation, protocol noncompliance, or withdrawal of consent (Supplemental Fig. 1). If there was radiographic evidence of a response (not necessarily confirmed) of complete response (CR), partial response (PR), or stable disease (SD) and the patient's disease had not progressed or other discontinuation criteria had not been met, the administration of necitumumab plus *nab*-paclitaxel (doublet regimen) was maintained as 3-week cycles until there was radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. No other chemotherapy was permitted until radiographic documentation of PD.

Eligible patients were ≥18 years of age; had histologically or cytologically confirmed stage IV squamous NSCLC; had measurable disease at the time of study enrollment as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1); [15] had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; and were able to complete at least 2 cycles of treatment.

This study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline (E6), and applicable laws and regulations. All participants provided their informed consent, and the protocol was approved by the Ethical Review Board.

2.2. Efficacy and safety outcomes

The primary efficacy endpoint was the ORR, which was confirmed CR and PR associated with a treatment regimen of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab as first-line therapy in patients with stage IV squamous NSCLC. The key secondary efficacy endpoints were PFS, OS, and DCR. The safety endpoints were the incidence of treatment-related adverse events, which were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Other secondary endpoints were pharmacokinetics and immunogenicity of necitumumab. The biomarkers related to EGFR pathway were also explored in this study.

2.3. Statistical analysis

The ORR and DCR were analyzed in the patients (qualified population) who were treated with any amount of study drug and had complete radiographic assessment at baseline. The ORR denominator included all qualified patients, whereas the numerator represented patients with a confirmed best overall tumor response of PR or CR per RECIST 1.1. The DCR denominator included all qualified patients; the numerator counted those with confirmed best tumor response of SD, PR, or CR per RESIST 1.1.

Analyses of efficacy for OS and PFS included only patients who were treated with any amount of study drug (safety population). The OS duration was measured from the date of the first dose of necitimumab, *nab*-paclitaxel, and carboplatin to the date of death from any cause. PFS was defined as the time from the date of the first dose of necitimumab, *nab*-paclitaxel, and carboplatin until the first observation of objective, radiographically documented PD as defined by RESIST 1.1 or death from any cause, whichever came first.

2.4. Other analyses

Safety analyses were based on the safety population. The number of patients who experienced a treatment-emergent adverse event (TEAE), serious adverse event (SAE), or adverse event (AE) related to study treatment; died; or discontinued from study treatment due to an AE were reported and graded according to NCI CTCAE v4.0.

To assess EGFR protein expression, immunohistochemistry (IHC) assays were performed on formalin-fixed, paraffin-embedded tumor tissue slides read by a board-certified pathologist. Positive staining was defined as immunoreactivity of tumor cell membranes at any intensity (1+, 2+, or 3+) in > 1% of cells, whether it was complete or incomplete circumferential staining. Negative staining was defined as immunoreactivity of tumor cell membranes at any intensity (1+, 2+, or 3+) in ≤1% of cells. EGFR biomarker analysis was based on the translational research (TR) population, de due to an AE were reported and graded according to NCI CTCAE v4.0.

To assess EGFR protein expression, immunohistochemistry (IHC) assays were performed on formalin-fixed, paraffin-embedded tumor tissue slides read by a board-certified pathologist. Positive staining was defined as immunoreactivity of tumor cell membranes at any intensity (1+, 2+, or 3+) in > 1% of cells, whether it was complete or incomplete circumferential staining. Negative staining was defined as immunoreactivity of tumor cell membranes at any intensity (1+, 2+, or 3+) in ≤1% of cells. EGFR biomarker analysis was based on the translational research (TR) population, defined as qualified patients for whom a valid biomarker assay result had been obtained. The ORR in each biomarker subgroup (EGFR protein expression positive and negative) was calculated.

The presence of anti-drug antibody (ADA) and neutralizing antibodies to necitumumab was assessed using 2 separate validated enzyme-linked immunosorbent assays (ELISAs) in accordance with the US Food and Drug Administration Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins [16]. ELISAs assessed samples at screening and subsequently confirmed; positive results for anti-necitumumab antibodies were reported as detected. Of those that were detected, titers were further assessed and

Table 1
Patients Demographics and Disease Characteristics (Safety Population).

Parameter	Necitumab + *Nab*-paclitaxel + Carboplatin (N = 54)
Age, mean (SD)	65.96 (7.5)
Gender, n (%)	
Female	12 (22.2)
Male	42 (77.8)
Race, n (%)	
White	53 (98.1)
Black	1 (1.9)
Region, n (%)	
Europe	39 (72.2)
United States	15 (27.8)
Stage IV	54 (100)
Squamous histology	54 (100)
ECOG PS	
0	12 (22.2)
1	42 (77.8)
Prior systemic therapy, n (%)	6 (11.1)
Neoadjuvant	1 (1.9)
Adjuvant	5 (9.3)
Prior radiotherapy, n (%)	14 (25.9)
Prior anti-cancer surgery, n (%)	18 (33.3)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

neutralized by an ADA assay.

3. Results

3.1. Patient disposition and characteristics

Fifty-four patients were enrolled from 12 October 2015 at sites in Spain, Germany, Greece, and the United States. Of the 54 patients included in the safety population, 51 patients were included in the qualified patient population, according to the definition described in the safety analysis section of the Methods section. At the time of data cut-off (29 January 2018), 11 patients remained on treatment. The reasons for study treatment discontinuation among the 54 patients were PD (25 patients [46.3%]), death (9 patients [16.7%]), withdrawal by subject (4 patients [7.4%]), AEs (3 patients [5.6%]), and physician decision (2 patients [3.7%]).

The majority of the patients were male (n = 42 [77.8%]) and White (n = 53 [98.1%]) and had an ECOG PS of 1 (stage IV NSCLC squamous histology). Of patients included in this study, 11.1% received prior neoadjuvant (1.9%) or adjuvant (9.3%) therapy (Table 1).

3.2. Efficacy

In the qualified population (51 patients), the ORR was 51% (n = 26) and the DCR was 78.4% (n = 40) (Table 2). In the safety population (54 patients), median OS was 15.5 months (95% confidence interval [CI]: 10.18–not calculable [NC]) (Fig. 1A), and the OS rate at 12 months was 50.4% (95% CI: 29.0–68.4). In the same population, median PFS was 5.6 months (95% CI: 4.24–7.69)] (Fig. 1B). The robustness of these results was confirmed by sensitivity analyses with restricted censoring (median, 5.8 months [95% CI: 4.24–7.69]) (data not shown).

Table 2
Tumor Response in Patients Treated With Necitumab, *Nab*-paclitaxel, and Carboplatin.

Parameter	Necitumab + *Nab*-paclitaxel + Carboplatin (N = 51)
Best overall response, n (%)	
Complete response (CR)	0 (0)
Partial response (PR)	26 (51.0)
Stable disease (SD)	14 (27.5)
Progressive disease (PD)	3 (5.9)
Nonevaluable	8 (15.7)
Overall response rate (CR/PR)	26 (51.0)
Disease control rate (CR/PR/SD)	40 (78.4)

3.3. Treatment exposure

Overall, the median duration of exposure was 18.6 weeks (range, 2–53 weeks) for necitumumab, 20.3 weeks (range, 1–53 weeks) for *nab*-paclitaxel, and 13 weeks (range, 3–17.86 weeks) for carboplatin. The difference in duration of individual drug exposure came from the protocol allowance of continuation of the other agents when a study drug is discontinued. The median number of cycles of necitumumab and *nab*-paclitaxel received overall per patient was 6 (range, 1–16). The median number of cycles of carboplatin received overall per patient was 4 (range, 1–4).

3.4. Safety

All patients reported at least 1 TEAE, including decreased neutrophil count (55.6%), fatigue (55.6%), and anemia (57.4%) (Table 3). Of the 54 patients, the majority (n = 43 [79.6%]) experienced drug-related CTCAE grade ≥3 TEAEs (Table 3). Overall, the most common study drug–related CTCAE grade ≥3 TEAEs (occurring in ≥10% of patients) were neutrophil count decreased (38.9%), fatigue (18.5%), anemia (16.7%), and decreased white blood cell count (11.1%).

Overall, a total of 20 patients (37%) had SAEs, Most of the patients with SAEs had these events during the initial 4 cycles of induction therapy which consisted of necitumumab in combination with *nab*-paclitaxel and carboplatin than in the maintenance phase (n = 18 [33.3%] vs. n = 5 [14.7%])

Of the 54 patients, a total of 7 patients discontinued study treatment due to AEs, and 4 deaths (7.4%) occurred due to AEs during the study. The AEs leading to death for those 4 patients were chronic obstructive pulmonary disease, interstitial lung disease, multiple organ dysfunction syndrome, and pneumonia. None of these AEs were considered to be related to the study drugs, and no venous thromboembolisms (VTEs) or arterial thromboembolisms (ATEs) were reported in relation to death.

After study therapy discontinuation, 29.6% of patients received at least 1 additional systemic anticancer therapy (Supplemental Table 1). Nivolumab (n = 8 [14.8%]) and atezolizumab (n = 6 [11.1%]) were the most commonly used.

3.5. Biomarkers and immunogenicity

A total of 44 patients (86.3% of the qualified population) had a valid EGFR IHC assay result available and were included in the TR population. Of these patients (n = 44), 39 patients (88.6%) were EGFR expression positive and 5 patients (11.4%) were EGFR expression negative. The ORR was 53.8% (95% CI: 38.6–68.4) in the patients with EGFR expression positive and 0% in the patients with EGFR expression negative. Given the small sample size with these subgroups, the relationship between the tumor response and EGFR expression was not conclusive. With respect to immunogenicity, 2 patients experienced a grade 3 hypersensitivity and infusion-related reaction (IRR) that was considered to be related to study treatment per assessment; however, no treatment-emergent ADA was detected in these patients.

4. Discussion

In this study of first-line treatment for stage IV squamous NSCLC patients, most of the efficacy outcomes (ORR: 51%; median PFS: 5.6 months) of necitumumab in combination with *nab*-paclitaxel and

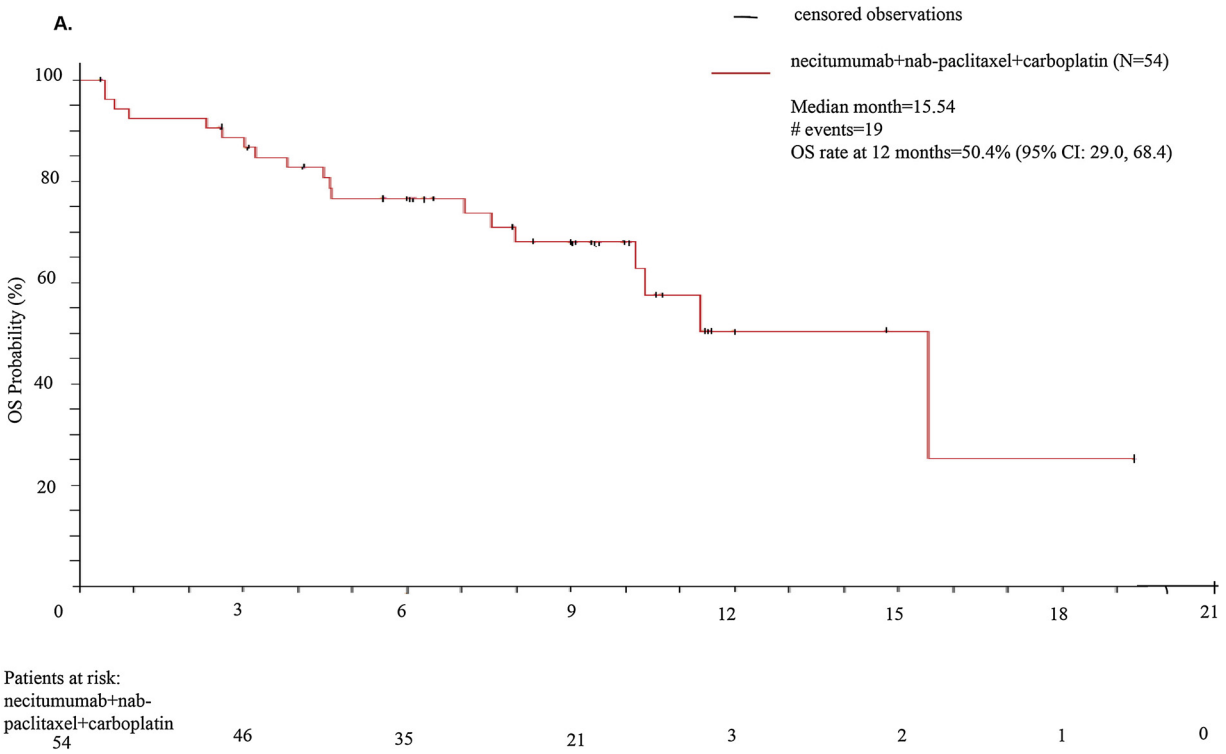

Fig. 1. Overall survival (A) and progression-free survival (B) in patients treated with necitumab, *nab*-paclitaxel, and carboplatin (safety population).

carboplatin were in the range of those in previous studies of necitumumab plus chemotherapy. The ORR and PFS of necitumumab plus gemcitabine/cisplatin in SQUIRE [11] and necitumumab plus paclitaxel/carboplatin in Spigel et al. [17] (NCT01769391) were 51% and 48.9%, respectively, and median PFS of the necitumumab combinations in those 2 studies were 5.7 and 5.4 months, respectively. The median OS (15.5 months) was numerically greater in this study compared with the outcome of reference studies; 13.2 months in patients treated with necitumumab plus paclitaxel/carboplatin in Spigel et al. [17] and 11.5 months with necitumumab plus gemcitabine/cisplatin in SQUIRE [11]. This may be attributed to the relatively higher proportion of patients (25.9% [14/54]) who received subsequent therapies with anti-PD-(L)1 agents. Approximately 30% of patients (16/54) who discontinued necitimumab/*nab*-paclitaxel/carboplatin had subsequent therapy.

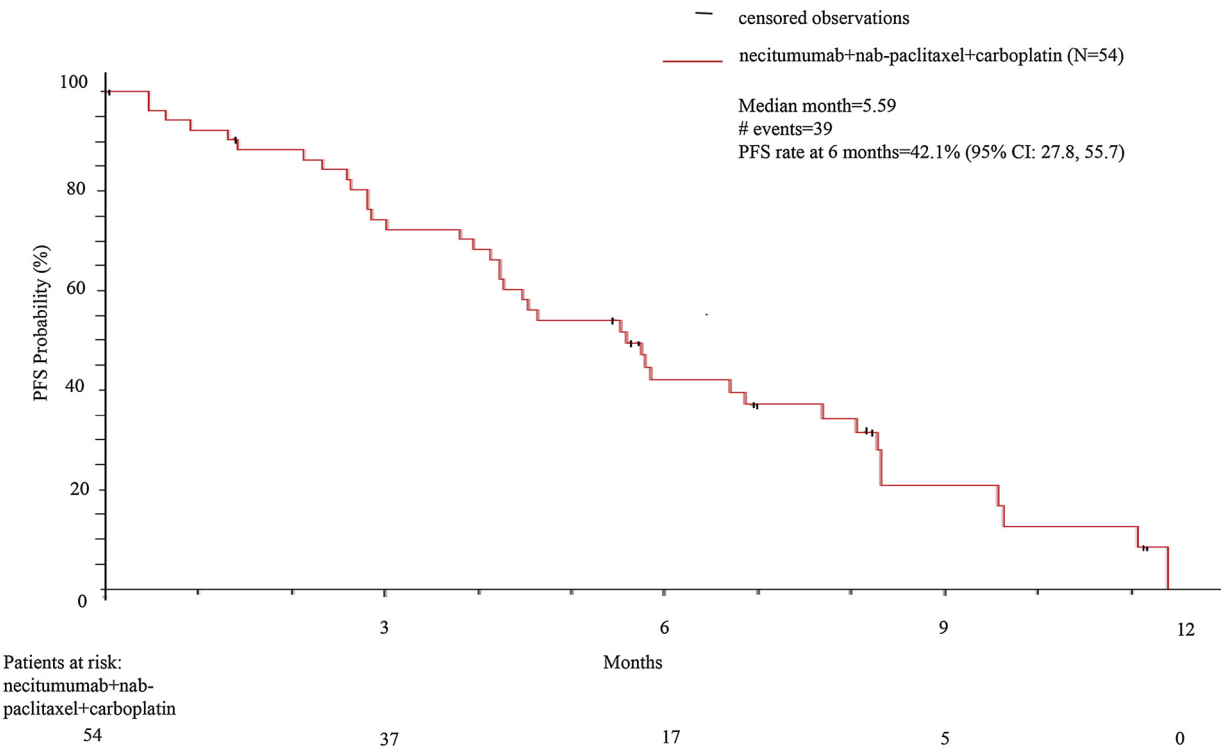

Fig. 1. (*continued*)

Table 3
Summary of Treatment-Emergent Adverse Events in Patients Treated With Necitumab, *Nab*-paclitaxel, and Carboplatin.

Preferred Term	Necitumab + *Nab*-paclitaxel + Carboplatin (N = 54)	
	All Grades	Grade ≥3
TEAE ≥1	54 (100)	43 (79.6)
Anemia	31 (57.4)	9 (16.7)
Fatigue	30 (55.6)	10 (18.5)
Neutrophil count decreased	30 (55.6)	21 (38.9)
Hypomagnesemia	24 (44.4)	5 (9.3)
Rash	21 (38.9)	4 (7.4)
Dermatitis acneiform	18 (33.3)	2 (3.7)
Platelet count decreased	17 (31.5)	2 (3.7)
Nausea	16 (29.6)	2 (3.7)
Diarrhea	14 (25.9)	3 (5.6)
White blood cell count decreased	12 (22.2)	6 (11.1)
Decreased appetite	11 (20.4)	3 (5.6)
Peripheral sensory neuropathy	11 (20.4)	2 (3.7)
Vomiting	11 (20.4)	1 (1.9)
Constipation	11 (20.4)	0

Data are presented as n (%).
Abbreviation: TEAE, treatment-emergent adverse event.

The safety profile of necitumumab in combination with *nab*-paclitaxel and carboplatin was consistent with those of individual study drugs [8,13,14]. The safety findings were predictable and manageable, with no new critical safety concerns identified. Consistent with the safety profile of anti-EGFR, mAbs, skin reactions, and hypomagnesemia occurred at a higher incidence. There were no events with respect to fatal VTE or ATE. Hypersensitivity or IRR was less commonly observed when compared with results from the Spigel et al. [17] study and SQUIRE [11].

Although most NSCLC tumors express the EGFR protein, especially squamous cell types [18], no clinically meaningful conclusions can be drawn from our exploratory analysis of EGFR protein expression due to the small sample size overall and in the EGFR-negative subpopulation. Overall, the rate of ADA formation was low and comparable with the rates observed in SQUIRE, which reported 15% of positive necitumumab antibodies in patients treated with necitimumab/gemcitabine/cisplatin at any time during the study [11]. Further, this is a valid treatment strategy for a small subset of patients who are ineligible for immunotherapy due to pre-existing autoimmunity, solid organ transplant, or prior immune-related toxicity or who progress on first-line single-agent treatment with pembrolizumab, for which alternate treatment strategies are needed.

5. Conclusions

In patients with advanced squamous NSCLC, necitumumab and *nab*-paclitaxel plus carboplatin first-line therapy produced favorable efficacy outcomes with manageable toxicity in patients with stage IV squamous NSCLC. The safety profile was fairly comparable with previous necitumumab combination studies in lung cancer.

Funding

This study was supported by Eli Lilly and Company.

Declaration of Competing Interest

Jong Seok and Wei Zhang are employees and shareholders of Eli Lilly and Company. Liza Villaruz, Manuel Cobo, and Konstantinos Syrigos have nothing to discl8.009.

References

[1] E. Suarez, B.E.C. Knollmann-Ritschel, Squamous cell carcinoma of the lung, Acad. Path. 4 (2017) 1–4.
[2] American Cancer Society, About Non-small Cell Lung Cancer, (2016) https://www.cancer.org/content/dam/CRC/PDF/Public/8703.00.pdf.
[3] J.R. Brahmer, G. Ramaswamy, R.A. Anders, et al., The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC), J. Immunother. Cancer 6 (2018) 75.
[4] B.A. Chan, B.G. Hughes, Targeted therapy for non-small cell lung cancer: current standards and the promise of the future, Transl. Lung Cancer Res. 4 (2015) 36–54.
[5] D.S. Ettinger, D.E. Wood, D.L. Aisner, et al., Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. 15 (2017) 504–535.
[6] Y. Yarden, G. Pines, The ERBB network: at last, cancer therapy meets systems biology, Nat. Rev. Cancer 12 (2012) 553–563.
[7] C.L. Arteaga, J.A. Engelman, ERBB receptors: from oncogene discovery to basic science to methcanism-based cancer therapeutics, Cancer Cell 25 (2014) 282–303.
[8] Eli Lilly and Company, Portrazza (necitumumab) Prescribing Information, (2015) http://pi.lilly.com/us/portrazza-uspi.pdf.
[9] R. Dienstmann, J. Tabemero, Necitumumab, a fully human IgG1 mAb directed against the EGFR for the potential treatment of cancer, Opin. Invest. Drugs 11 (2010) 1434–1441.
[10] L. Greillier, P. Tomasini, F. Barlesi, Necitumumab for non-small cell lung cancer, Expert Opin. Biol. Ther. 15 (2015) 1–9.
[11] N. Thatcher, F.R. Hirsch, A.V. Luft, et al., Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial, Lancet Oncol. 16 (2015) 763–774.
[12] M.A. Socinski, I. Bondarenko, N.A. Karaseva, et al., Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial, J. Clin. Oncol. 30 (2012) 2055–2062.
[13] Celgene Corporation, Abraxane (paclitaxel Protein-bound Particles) Prescribing Information, (2018) https://media.celgene.com/content/uploads/abraxane-pi.pdf.
[14] Hospira, Carboplatin Prescribing Information, (2018) http://labeling.pfizer.com/ShowLabeling.aspx?id=4379.
[15] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009) 228–247.
[16] United States Food and Drug Administration, Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, (2016) https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf.
[17] D.R. Spigel, A. Luft, H. Depenbrock, et al., An open-label, randomized, controlled phase II study of paclitaxel-carboplatin chemotherapy with necitiumumab versus paclitaxel-carboplatin alone in first-line treatment of patients with stage IV squamous non-small-cell lung cancer, Clin. Lung Cancer 18 (2017) 480–488.
[18] A.V. López-Malpartida, M.D. Ludeña, G. Varela, J. García Pichel, Differential ErbB receptor expression and intracellular signaling activity in lung adenocarcinomas and squamous cell carcinomas, Lung Cancer 65 (2009) 25–33.